Approaches to Performing Metabolite Elucidation: One Key to Success in Drug Discovery and Development

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Absorption, distribution, metabolism, excretion, and toxicology (ADMET) studies are widely used in drug discovery and development to help obtain the optimal balance of properties necessary to convert lead compounds into drugs that are safe and effective for human use. Drug discovery efforts have been aimed at identifying and addressing metabolism issues at the earliest possible stage, by developing and applying innovative liquid chromatography–mass spectrometry (LC-MS)-based techniques and instrumentation, which are both faster and more accurate than prior techniques. Such new approaches are demonstrating considerable potential to improve the overall safety profile of drug candidates throughout the drug discovery and development process. These emerging techniques streamline and accelerate the process by eliminating potentially harmful candidates earlier and improving the safety of new drugs. In the area of drug metabolism, for example, revolutionary changes have been achieved by the combination of LC-MS with innovative instrumentation such as triple quadrupoles, ion traps, Orbitrap, and time-of-flight mass spectrometry. In turn, most ADMET studies have come to rely on LC-MS for the analysis of an ever-increasing workload of potential candidates. This chapter provides a discussion on the importance of LC-MS in supporting metabolic activation testing, metabolite characterization, and radiolabeled-drug testing.

1 INTRODUCTION

Mass spectrometry (MS) and nuclear magnetic resonance (NMR) are critical to the success of such ADMET studies. NMR spectroscopic techniques are most often used to confirm and elucidate metabolite identification in drug metabolism studies. Liquid

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